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Body weight reduction and metformin: Roles in polycystic ovary syndrome

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Abstract

Background and objectives: Polycystic ovary syndrome (PCOS) is a common problem in women at fertile age. A prospective study was conducted to clarify the pathophysiological responses during an application of insulin sensitizer, metformin and weight reduction therapy at the Gynecology Center in Ohud hospital, in AL-Madinah AL-Munawarah, Kingdom of Saudi Arabia. **Methodology:** Twenty healthy women served as controls and 180 PCOS women divided into three groups participated in the study. First group was treated with Clomid citrate 100 mg/day from the 2nd day of menses to the 6th day plus gonadotrophin from day three to the 13th. Group II was treated as group I plus 850 mg metformin twice a day and group III was treated as group I plus weight reduction. Clinical symptoms, menstrual pattern, hirsutism, blood glucose, body mass index, waist-to-hip ratio, insulin, hormonal, and lipid profiles were assessed pre- and post treatment. Insulin resistance was calculated. **Results:** PCOS women had significantly higher values than the healthy women in most of the measurements. Metformin and weight reduction therapy resulted in a significant decrease in the fasting insulin, glucose/insulin ratio and HOMA-IR. Metformin and weight reduction therapy resulted in a significant decrease in the lipid parameters, testosterone, LH/FSH ratio, SHBG, and prolactin levels. HOMA-IR was significantly higher in women with PCOS. HOMA-IR was positively correlated with testosterone, estradiol, TG, total cholesterol and LDL-cholesterol parameters, and negatively correlated with HDL-cholesterol and FSH levels. **Conclusion:** Metformin therapy and weight reduction had favorable influences on the basic metabolic and hormonal profiles in women with PCOS and that metformin and lifestyle modification (weight reduction via diet restriction or exercise) resulted in a significantly greater weight loss than hormonal therapy alone. Metformin and weight reduction therapy decreased also hyperandrogenism and insulin resistance.

Keywords: HOMA-IR; Metformin; Polycystic ovary syndrome; Weight reduction; Lipid profiles; Insulin; Testosterone

1. Introduction

Polycystic ovarian syndrome (also referred to as Stein–Leventhal syndrome or hyperandrogenic chronic anovulation) is an endocrine disorder found in 5–10% women [1].

The disease is manifested clinically by irregular menstrual cycles, signs of androgen excess including amenorrhea, or oligomenorrhea, hirsutism, reduced fertility, obesity, multiple cysts in the ovaries, insulin resistance, acne and male pattern alopecia [2,3].

Polycystic ovary syndrome is frequently associated with various patterns of dyslipidemia including low high-density lipoprotein cholesterol (HDL-C), high levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) [4]. Although the data from large series suggest that the mean values for circulating lipids in women with PCOS are in normal limits, up to 70% of patients have at least one abnormal lipid level according to NCEPATPIII criteria [5]. Normal ovulatory mechanism which includes selection of an ovarian follicle which grows in response to appropriate secretion of FSH become dominant and ovulates, gets disturbed in women with PCOS due to androgen excess and

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hyperestrogenism [6]. Ovarian overproduction of androgens contributes to hyperinsulism and raised insulin levels which are recognized as important features in PCOS [7]. Insulin lowering therapies such as metformin can bring improvement in insulin resistance and ovarian hyperandrogenism [3]. It has also been shown that the ovulatory response to clomiphene for induction can be increased in PCOS by decreasing insulin secretion with metformin [8]. The association of insulin resistance contributing to anovulation has led to normal and promising therapy administering insulin sensitizing agent to women with PCOS in order to restore ovulation and enhance fertility [9].

Despite being one of the most common endocrinopathies, a comprehensive explanation of pathophysiology is still lacking. The heterogeneity of PCOS may well reflect multiple pathophysiological mechanisms, but the definition of each contributing mechanism has been slow to emerge. Traditionally, it has been useful to consider the PCOS as the result of a 'vicious cycle', which can be initiated at any one of many entry points. Altered function at any point in the cycle leads to the same result: ovarian androgen excess and anovulation [10].

It is a complex disease, and several pathophysiologic mechanisms seem to be involved. Insulin resistance and hyperinsulinemia play a central role in the pathogenesis [11–17], and women with PCOS are considered at increased risk of developing impaired glucose tolerance and type 2 diabetes mellitus [18–20].

Metformin belongs to the biguanide class of oral antidiabetic agents that improve glucose levels. It is widely used in the treatment of both type 2 diabetes mellitus and has been recently proposed as a first-line treatment in obese or overweight PCOS women with hyperinsulinemia [21,22]. A link between disturbed insulin action and PCOS was first highlighted in 1980 [23], and subsequent studies have shown that insulin resistance is an integral feature of PCOS [24].

The associated hyperinsulinemia may promote abnormal ovarian androgen secretion and therewith abnormal follicular development, leading to dysfunctional ovarian and menstrual activity [25]. As a consequence of insulin resistance, women with PCOS exhibit a greater risk for dyslipidemia [26], coagulation disorders and endothelial dysfunction [5], increased incidence of hypertension [27], and type 2 diabetes mellitus [28,29] in later life, and those are established risk factors for cardiovascular disease [30].

The aim of the present study was to clarify further the hormonal and metabolic disturbances and the effects of weight reduction and glucose level correction in PCOS women in fertile age.

2. Materials and methods

Our 6 months prospective, open clinical study was carried out after the protocol approval by the Ethics Committee of Taibah University, and when written signed informed consents were obtained from each patient. The study was conducted according to the Declaration of Helsinki (as amended 1996).

Twenty healthy women and one hundred eighty women in the reproductive age with polycystic ovary syndrome (PCOS) were included in this study. The diagnostic criteria for the PCOS met the diagnostic criteria established by the 2003 European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine Consensus Conference based on the presence of two out of the following three criteria:

(1) Oligo or anovulation.
(2) Clinical and/or biochemical signs of hyperandrogenism.
(3) Polycystic ovaries.

In addition, the diagnosis of PCOS also was based on the exclusion of other PCOS-like syndromes, including adrenal dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, androgen – producing tumors, hyper-prolactinemia, and thyroid dysfunction.

2.1. Laboratory measurements

All the laboratory tests were repeated six months after the beginning of the treatment to determine the effect of these drugs on hormonal and biochemical parameters and on clinical presentations. All tests were done in the same laboratory using the same kits. All chemicals were of the highest purity available and purchased from Sigma–Aldrich Co. (St Louis, MO, USA).

Venous blood samples were collected from an anticubital vein between 08:00 and 10:00 a.m. after an overnight fasting on the third day of the menstrual cycle except in those with amenorrhea. The samples were centrifuged, aliquoted and immediately frozen at −80 °C for biochemical analysis.

2.2. Body mass index (BMI) and waist-to-hip ratio (WHR)

The women were weighed the nearest 0.1 kg, and height recorded to the nearest 0.5 cm. Body mass index of all women were calculated [BMI = body weight in kilograms (kg)/height in meter squared (m^2)]. The waist circumference was measured as the minimum value between the iliac crest and the lateral costal margin and the hip circumference was determined as the maximum value over the buttocks, using a 1 cm wide metal measuring tape. WHR was used as a measure of body fat distribution. The ratio of waist over hip circumferences was calculated. A BMI of <25 was considered normal; BMI of 25–29 was considered "overweight"; and a BMI of >30 was considered "obese".

2.3. Weight management

Weight reduction was achieved by consuming fewer Kcal than are required to meet energy needs. Our methods for